National Cancer Institute

Non-cancer Effects of Radiation

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

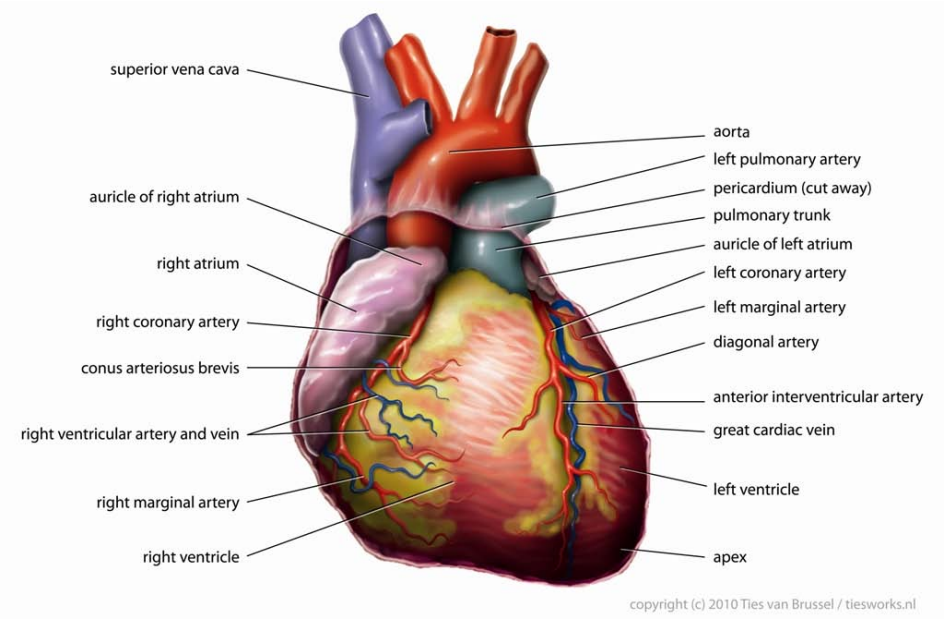
Topics

- Cardiovascular (circulatory) diseases
  - High therapeutic doses and heart disease/stroke
  - Risk at low doses
- Lens opacities - cataract

Cardiovascular diseases

- Major cause of morbidity/mortality - 30-50% of all deaths in many countries
  - Cancer contributes to 15-30%
- Heterogeneous disease entities, but
- 80-90% due to atherosclerosis, generalized underlying pathology, including
  - Ischemic heart disease, involving coronary arteries
  - Stroke

Heart diseases



- Ischemic heart disease, 80-90%
  - Late manifestation of coronary atherosclerosis
  - Myocardial infarction (MI), angina pectoris (AP), coronary heart disease (CHD)
- Hypertensive heart disease
  - Can lead to heart dysfunction, congestive heart failure (CHF)
- Valvular heart disease
  - Congenital, acquired (e.g., rheumatic HD)
- Pericarditis, myositis, etc.

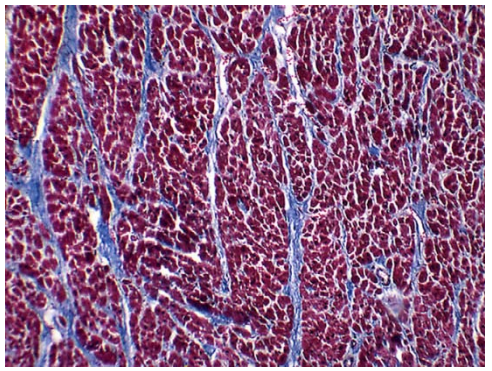
Heart disease following high-dose radiation therapy

- **Hodgkin's lymphoma**
- **Breast cancer**
- Testicular cancer
- Head/neck cancer

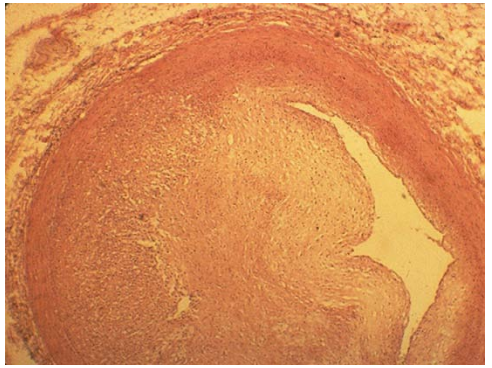
- **Peptic ulcer disease**

Heart disease & Hodgkin's lymphoma

- Cardiac toxicity of high-dose radiation had been known for some time
  - Late medical consequence of RT for Hodgkin's lymphoma
  - "Radiation-induced heart disease"
  - Pericarditis, myocarditis, etc, typically with fibrosis
- Emerging evidence of coronary heart disease (CHD) in following high-dose radiotherapy



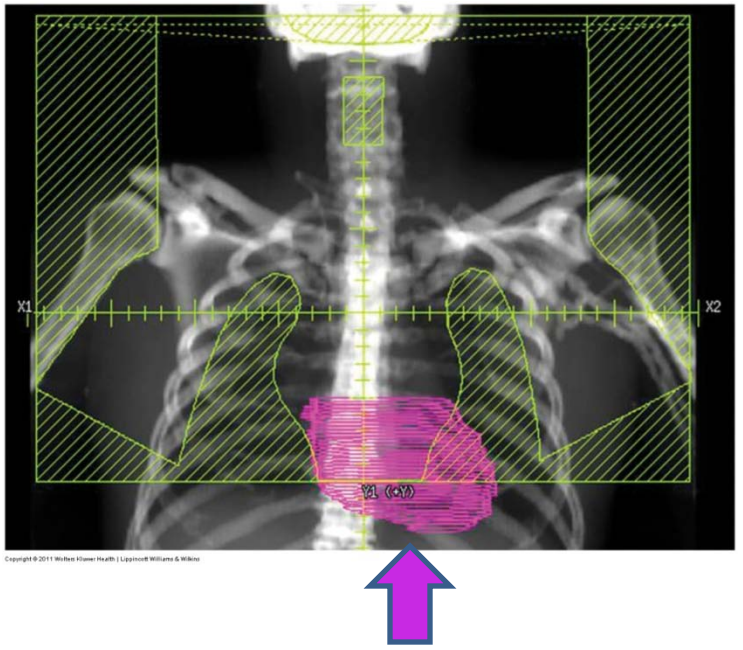
Fatal diffuse myocardial fibrosis after RT for HL



Coronary artery, 16 yr boy, after 40Gy, Mantle RT

Hodgkin's lymphoma

- Megavoltage Mantle field irradiation
  - Late 1960s: 40-44 Gy, chest
  - Mid-1970-94:
    - 30-40 Gy, RT alone
    - 30 Gy, with chemotherapy
  - Children after 1970s:
    - 15-25 Gy



Subcarinal block

Stanford Study: Pediatric and adult HL patients treated during 1960-90 (Hancock et al, 1993)

	Myocardial infarction		Other heart diseases	
	Obs/Exp	**SMR**	Obs/Exp	**SMR**
No RT	6/3.6	**1.7**	4/2.9	**1.4**
0-30 Gy	2/0.5	**4.2**	0/0.3	**-**
>30 Gy	47/13.3	**3.5**	29/8.4	**3.5**
Before 1972	26/7.0	**3.7**	23/4.3	**5.3**
After 1972*	23/6.8	**3.4**	6/4.3	**1.4**

* Routine blocking of left ventricular and carinal region introduced in 1972, limiting entire cardiac silhouette to 15 Gy

Stanford Study: Pediatric and adult HL patients - 2

	Myocardial infarction		Other heart diseases	
Age at RT	Obs/Exp	**SMR**	Obs/Exp	**SMR**
<20	6/0.1	**44.1**	4/0.2	**21.5**
20-29	8/1.1	**7.3**	7/0.8	**8.8**
30-39	14/2.7	**5.1**	7/1.5	**4.8**
40-49	9/3.0	**3.0**	3/1.6	**1.9**
50-59	12/6.8	**1.8**	8/4.6	**1.7**
Yrs after RT				
0-4	12/6.0	**2.0**	6/4.1	**1.5**
5-9	17/4.7	**3.6**	10/3.1	**3.2**
10-14	11/3.7	**3.0**	5/2.4	**2.1**
15-19	11/2.2	**5.0**	8/1.4	**5.8**
20+	4/0/7	**5.6**	4/0.5	**8.8**

Netherlands Study: 1,500 5-yr survivors of HL patients treated during 1965-95 (Aleman et al, 2007)

	Myocardial Infarction	Angina pectoris	Congestive heart failure
	Hazard ratio		
RT	2.4 (1.1-5.2)	4.9 (1.9-12)	7.4 (1.8-30)
Anthracycline CT	0.9 (0.5-1.6)	1.5 (0.9-2.5)	2.4 (1.4-3.6)
RT only	1.0	1.0	1.0
RT + CT, no anthracycline	1.2 (0.8-1.8)	0.7 (0.5-1.2)	1.3 (0.8-2.2)
RT + CT , anthracycline	1.0 (0.5-1.9)	1.3 (0.8-2.3)	2.8 (1.4-5.5)

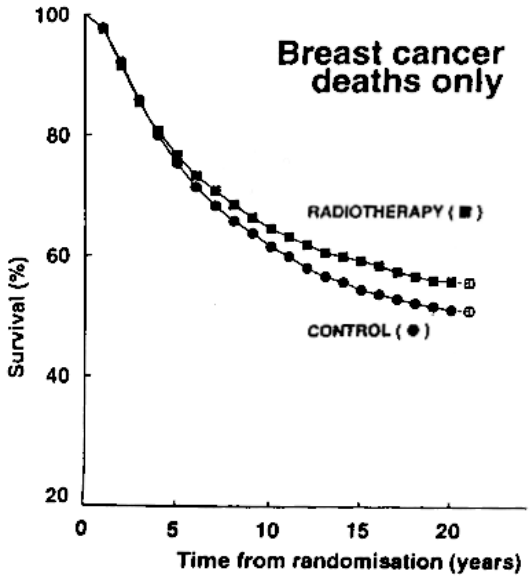
Heart disease in Hodgkin's lymphoma patients

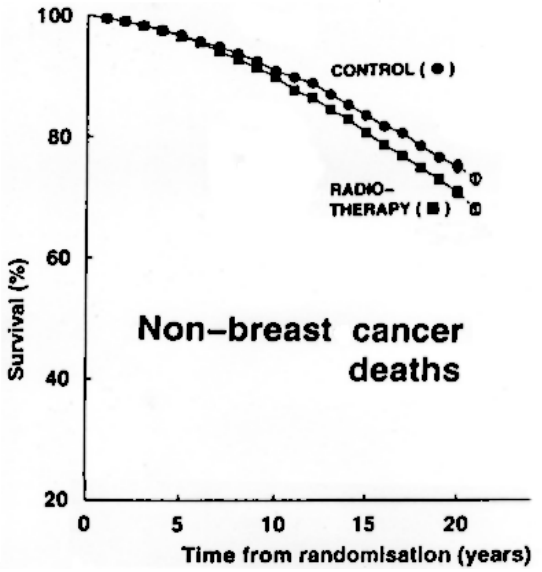
- Decreasing impact of RT for Hodgkin's lymphoma on classic "radiation-induced heart disease"; increasing impact on coronary heart disease
- Evolving RT and CT regimens requires continuing re-evaluation of the impact on heart disease
  - Decreasing effect from new RT techniques
  - Possibly increasing late effect of combined RT and CT

Heart disease and breast cancer

- For early-stage breast cancer, surgery is the primary treatment; followed by adjuvant radiotherapy and chemotherapy
- Compared to Hodgkin's lymphoma
  - Lower cardiac doses from breast cancer RT, but a larger exposed population
  - Lower heart disease risk and a longer latency
- Sources of risk data
  - Early-breast cancer randomized trials
  - Left-sided vs. right-sided breast cancer (laterality) studies

Early Breast Cancer Trialists' Collaborative Group (EBCTCG, 2005)

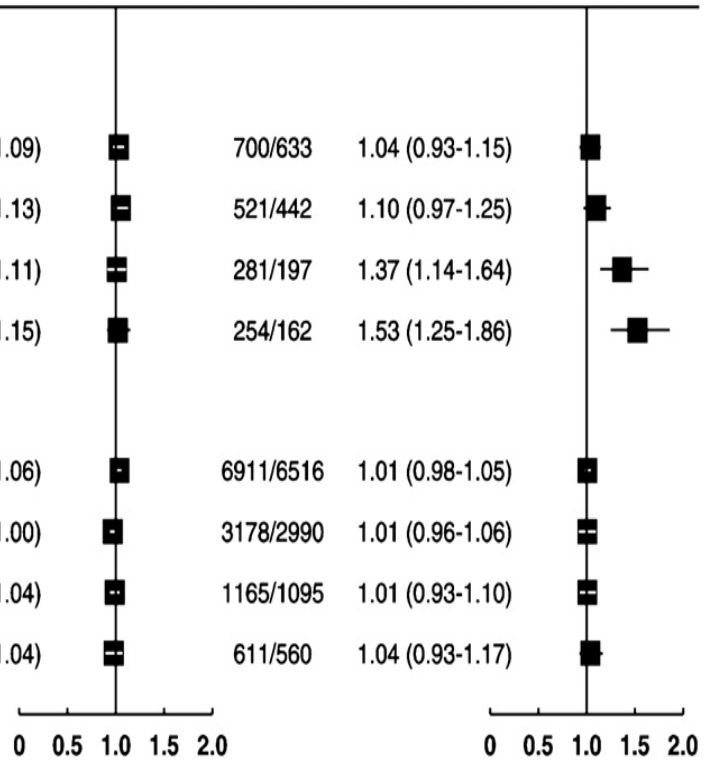


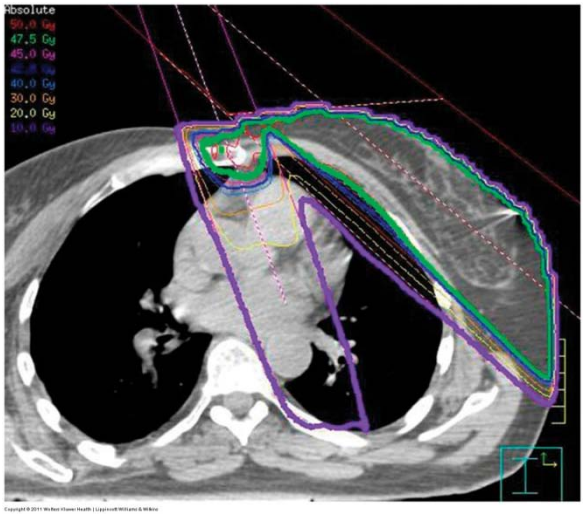


Cause of death	Number of deaths		**Ratio of annual death rates (SE)**
	Allocated to RT	Adjusted control	
Vascular	437	322	**1.30 (0.09)**
Non-vascular	382	313	**1.15 (0.09)**
Unknown	339	292	**1.09 (0.09)**
Total	1158	927	**1.18 (0.05)**

Left- vs. right-sided breast cancer (Darby, 2005)

Years since breast cancer diagnosis	No radiotherapy: No. of deaths left/right	No radiotherapy: Mortality ratio left versus right & 95% CI	Radiotherapy: No. of deaths left/right	Radiotherapy: Mortality ratio left versus right & 95% CI
Heart disease death				
< 5 years	2164/1972	1.03 (0.97-1.09)	700/633	1.04 (0.93-1.15)
5 - 9	1632/1479	1.05 (0.98-1.13)	521/442	1.10 (0.97-1.25)
10 - 14	806/758	1.01 (0.91-1.11)	281/197	1.37 (1.14-1.64)
15+	568/524	1.02 (0.91-1.15)	254/162	1.53 (1.25-1.86)
All other known causes				
< 5 years	14775/13522	1.04 (1.01-1.06)	6911/6516	1.01 (0.98-1.05)
5 - 9	8009/7863	0.97 (0.94-1.00)	3178/2990	1.01 (0.96-1.06)
10- 14	3472/3343	0.99 (0.94-1.04)	1165/1095	1.01 (0.93-1.10)
15+	2106/2040	0.98 (0.92-1.04)	611/560	1.04 (0.93-1.17)

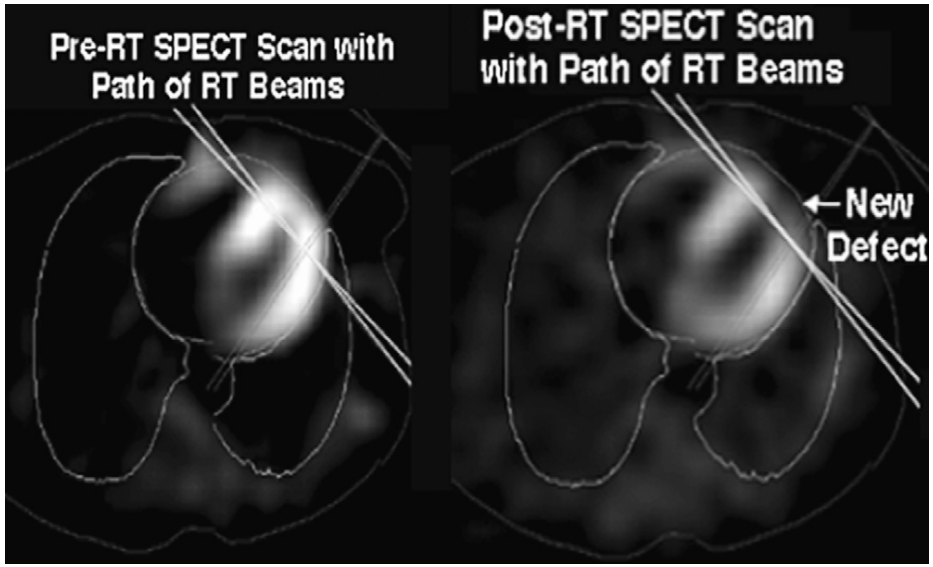




SEER, 1973-2001

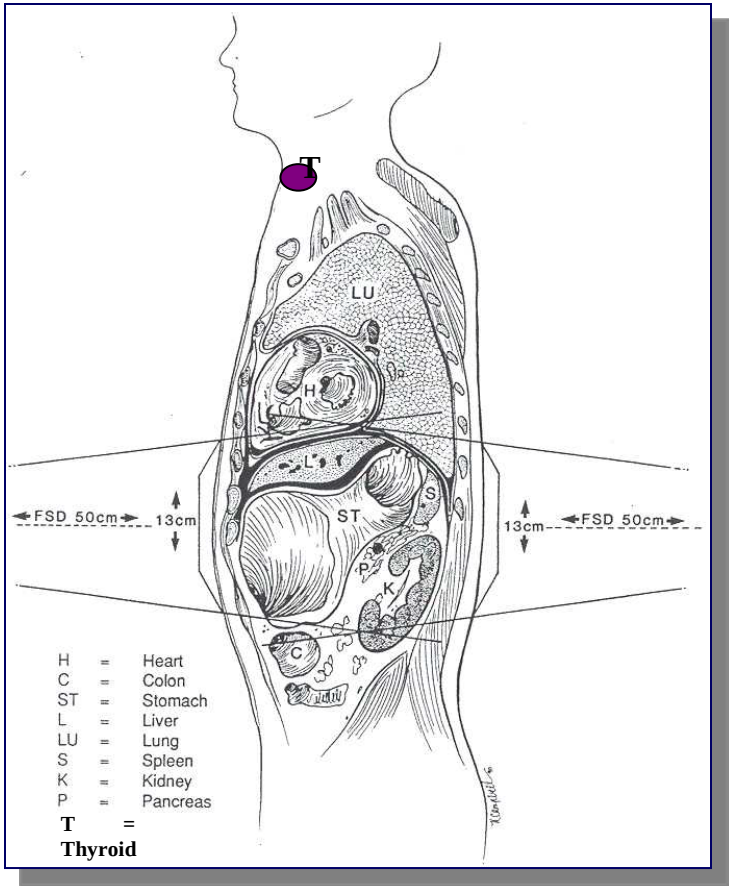
Imaging study following left breast cancer RT (Marks, 2005)

- Perfusion defects persisting 3-8 yrs after tangential photon irradiation for left breast cancer
  - Defects associated with modest wall motion abnormalities
  - Long-term clinical significance unclear



Heart disease following RT for peptic ulcer

- 3,600 peptic ulcer patients treated with RT
  - University of Chicago, 1940s-1960s
  - Daily fraction of 1.5 Gy for 6-14 days
- 5% of the heart in direct radiation field
  - Scattered radiation to the entire heart



Peptic ulcer disease cohort (Carr, 2005)

Weighted cardiac dose, Gy	In-field* dose, Gy	Coronary heart disease	Other heart disease
		RR	
0	0	1.0	1.0
0.1 – 1.9	0.86 – 9.1	1.0 (0.8-1.3)	1.5 (0.7-3.3)
2.0 – 2.5	9.2 – 11.7	1.2 (0.9-1.6)	0.5 (0.2-1.2)
2.6 – 3.0	12.0 – 13.9	1.5 (1.2-2.1)	0.7 (0.3-1.6)
3.1 – 7.6	14.4 – 35.6	1.5 (1.2-2.0)	1.7 (0.8-3.7)

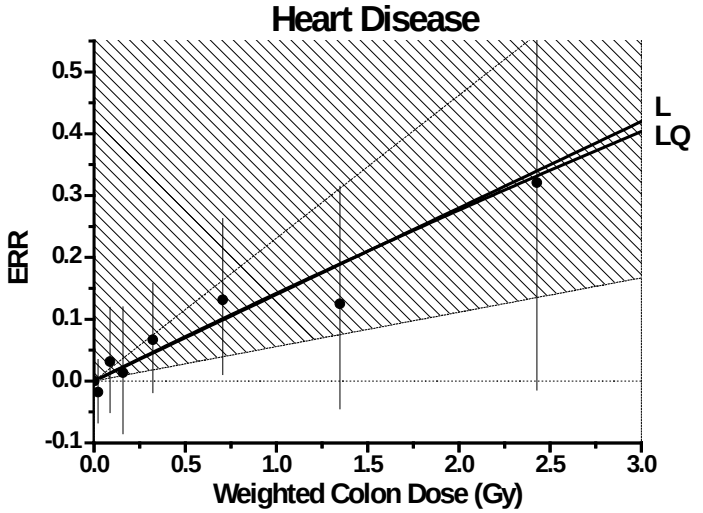
* 5% of the heart (apex) in the radiation field

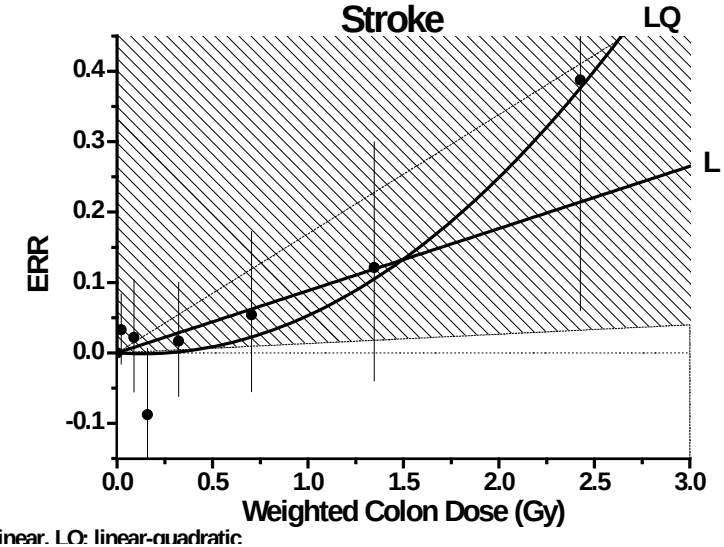
Cardiovascular disease at low doses

- Question
  - Dose response at doses <2-3 Gy, or even <1 Gy
- Sources
  - **Atomic-bomb survivors (LSS)**
  - Medically exposed populations
  - **Occupationally exposed populations**

LSS CVD mortality, 1950-2003 (Shimizu, 2010)

- Heart disease
  - ERR/Gy = 0.14 for full dose range, linear
  - ERRs similar for low dose range
  - But not significant in 0-0.5 Gy range
- Stroke
  - ERR/Gy = 0.9, linear
  - Possible upward curvature



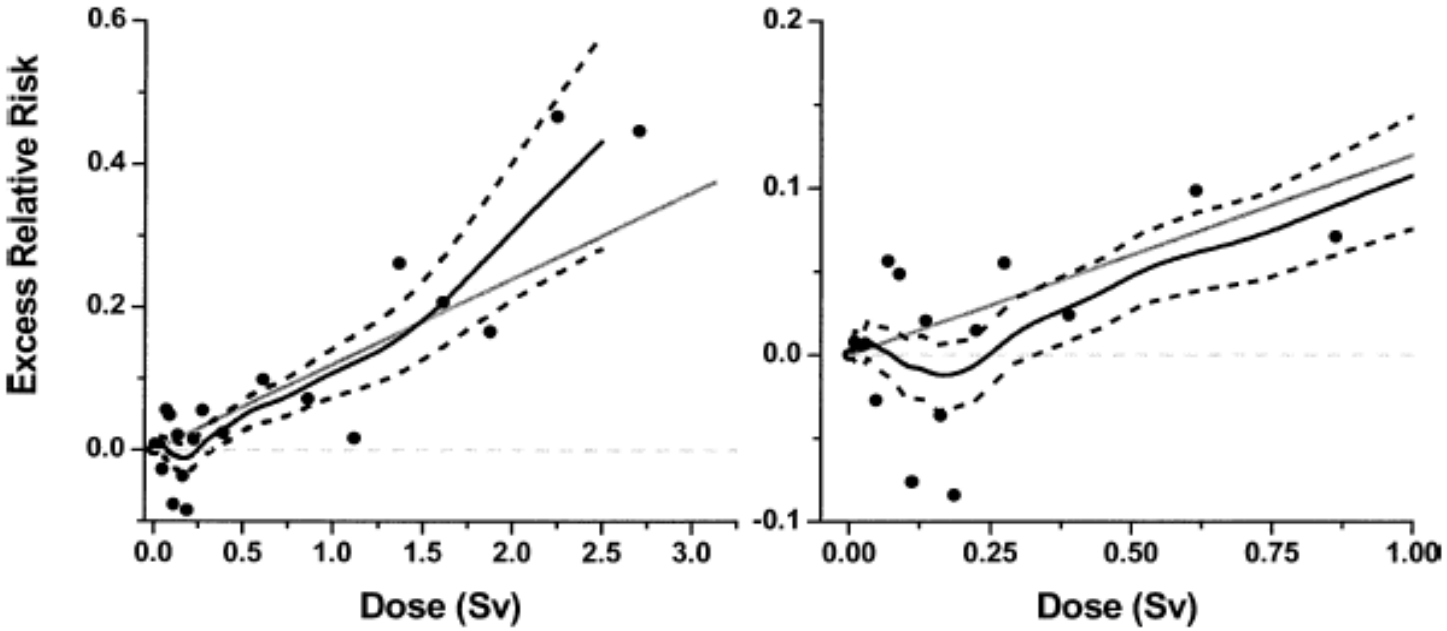


L: linear, LQ: linear-quadratic

LSS non-cancer disease mortality, 1968-97 (Preston, 2003)

Full dose range

Low dose range



LSS CVD mortality, 1950-2003 (Shimizu, 2010)

Cause of death	No of deaths	ERR/Gy, unadjusted*	ERR/Gy , adjusted*
Total	7,907	10.0	9.6
Stroke	3,366	8.1	7.2
Heart disease	4,204	12.2	12.3
Other circulatory	337	2.4	0.9

* Adjusted for possible confounders: smoking, drinking, household occupation, BMI, and diabetes

LSS non-cancer mortality, 1950-97 (Preston, 2003)

Dose, Gy	Obs	Exp	Excess
<0.005	13,832	13,954	0
0.005-0.1	11,633	11,442	17
0.1-0.2	2,163	2,235	17
0.2-0.5	2,423	2,347	47
0.5-1	1,161	1,075	61
1-2	506	467	68
2+	163	111	40
Total	31,881	31,631	**250**

Solid cancer deaths: 1,335 (**440** excess)

CVD risk in medically exposed populations

Cohort	Mean dose, Gy	ERR/Gy
TB fluoroscopy	0.84 (chest)	-0.11 (circulatory)
Ankylosing spondylitis	0.14 (brain) 2.49 (heart)	-2.43 (stroke) -0.01 (other circulatory)

CVD risk in occupationally exposed populations

Cohort	Mean dose, Gy	ERR/Gy	Comments
Canadian nuclear /other (n = 206,600)	0.063	2.3 (circulatory, male) 12.1 (circulatory, female)	
Russian Mayak (n = 12,200)	0.83 (γ) 0.52 (α)	0.109 (ischemic heart) 0.155 (cerebrovascular)	Adjusted for confounders
Russian Chernobyl (n = 61,000)	0.109	0.41 (ischemic heart) 0.45 (cerebrovascular)	Confounders?
IARC 15-Country (n = 275,300)	**0.0217**	**0.09 (circulatory), ns -0.01 (ischemic heart), ns 0.88 (cerebrovascular), ns**	**Dose range <0.5 Gy**
UK BNFL (n = 38,700)	**0.0569**	**0.70 (ischemic heart) 0.66 (cerebrovascular)**	**Dose range <0.729 Gy**

Worker studies for low-dose effects

- Advantages
  - Availability of film-badge measured doses
  - Large numbers of subjects
- Limitations
  - Limited data on possible confounders
    - Possible residual confounding from using proxy measures (e.g., employment status, socioeconomic status)

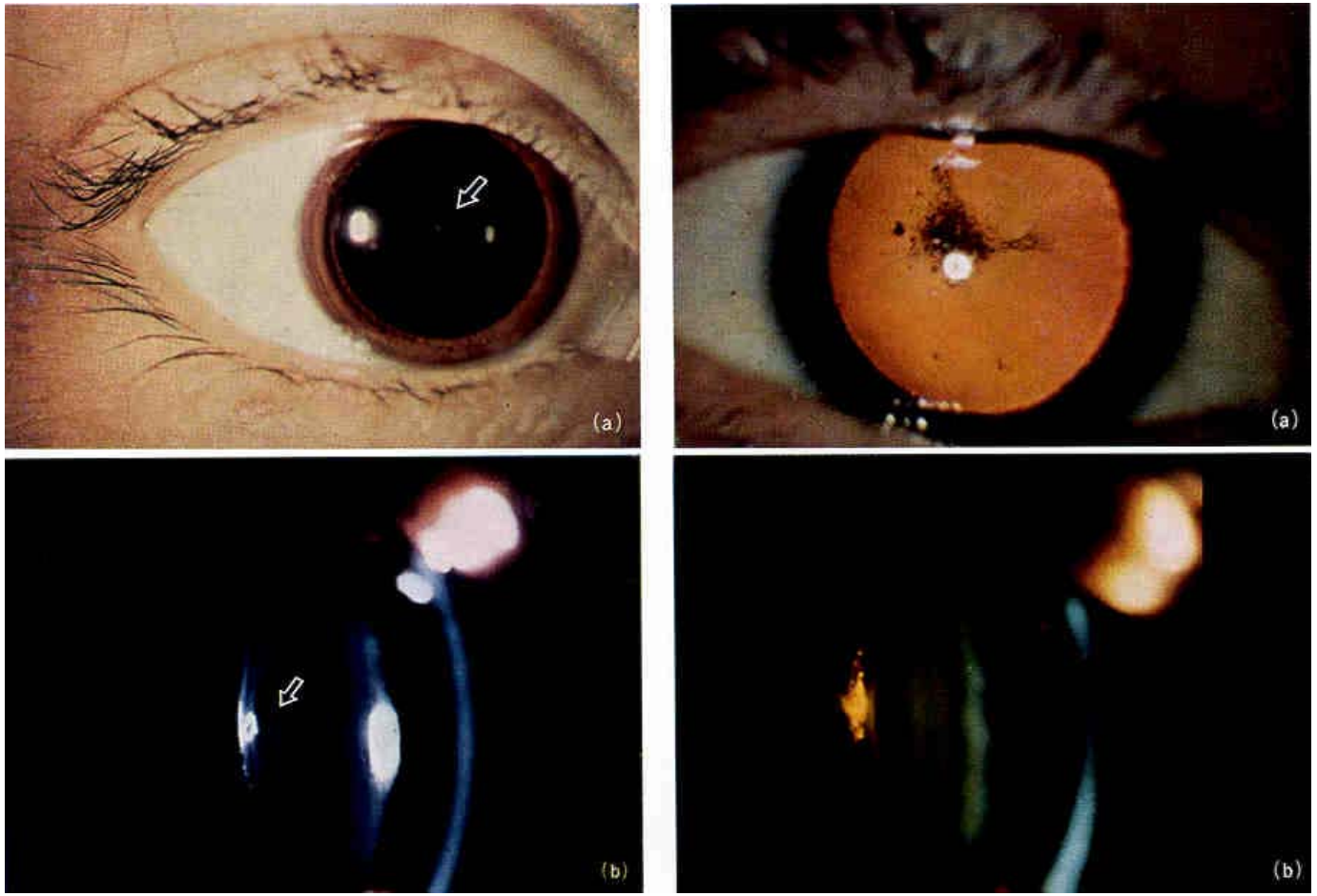
CVD risk summary

- There is a dose response for CVD in the 1-5 Gy range
- Excess relative risk for CVD is lower than for cancer but excess absolute risk is high
- Suggestion of a linear dose response, but the risk below 0.05 Gy is uncertain

Statement on Tissue Reactions
Approved by the Commission on April 21, 2011

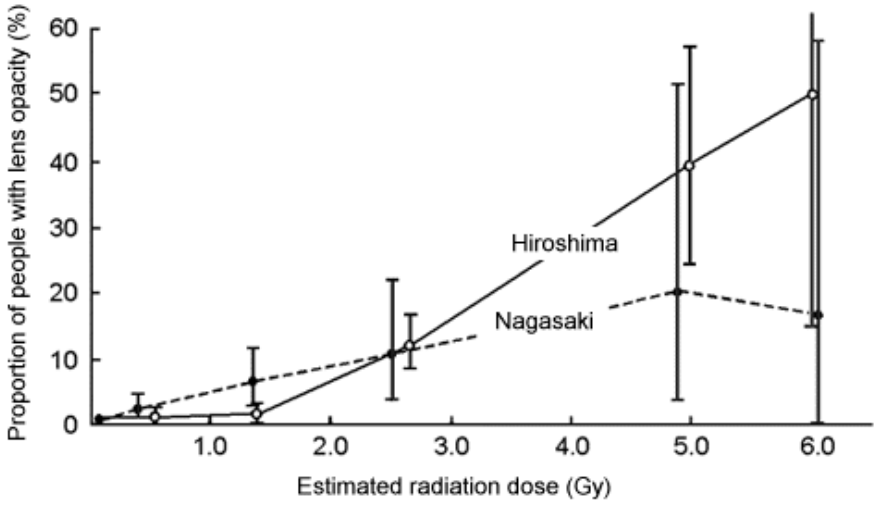
(4) Although uncertainty remains, medical practitioners should be made aware that the absorbed dose threshold for circulatory disease may be as low as 0.5 Gy to the heart or brain. Doses to patients of this magnitude could be reached during some complex interventional procedures, and therefore particular emphasis should be placed on optimisation in these circumstances.

Lens Opacities - Cataract



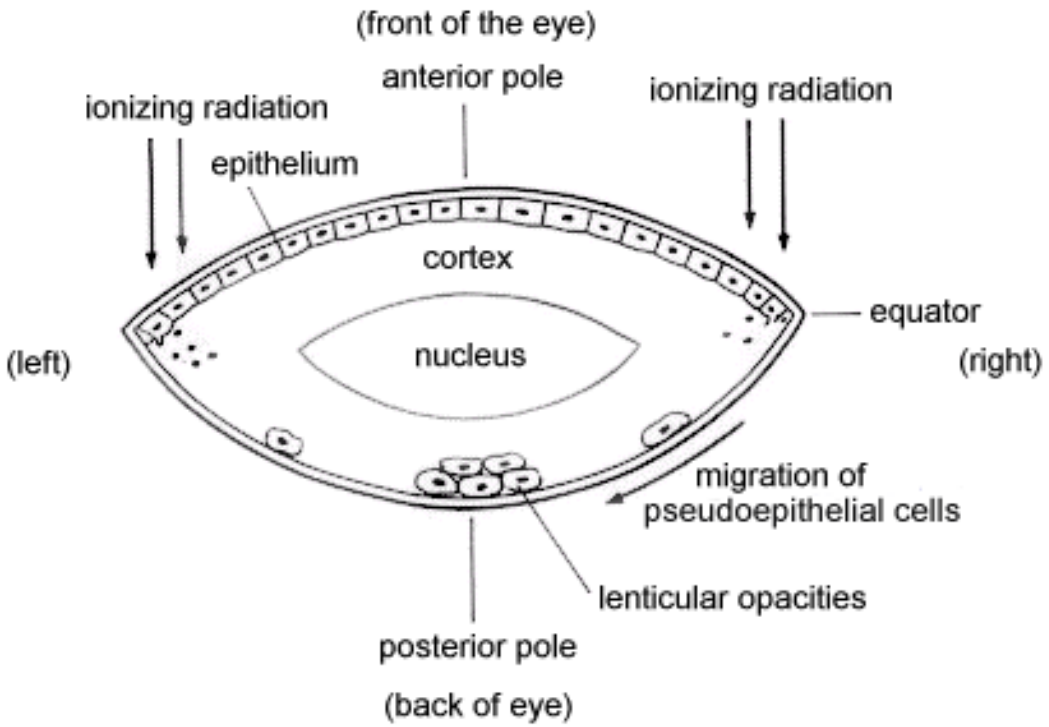
Lens opacities in A-bomb Survivors

- Early cases with very high doses observed appearing 3-4 years after the bombings
- In early 1960s, partial opacity, most often of posterior lens, detected by slit-lamp exams
  - Rarely causing visual impairment
  - Possible “threshold” dose level ~ 1.5 – 2 Sv



Posterior lenticular opacities: Possible mechanism

- Radiation especially harmful to dividing cells, at the equator
- Damaged cells move toward the rear of the lens before converging on the center
- Possible genomic involvement



Cataract types

- Three major types
  - Cortical: involves outer, recently formed lens fiber cells
  - Nuclear: developing first in inner embryological and fetal lens fiber cells
  - Posterior subcapsular (PSC): developing from dysplasia of transitional zone epithelial cells; resulting in an opacity at posterior pole

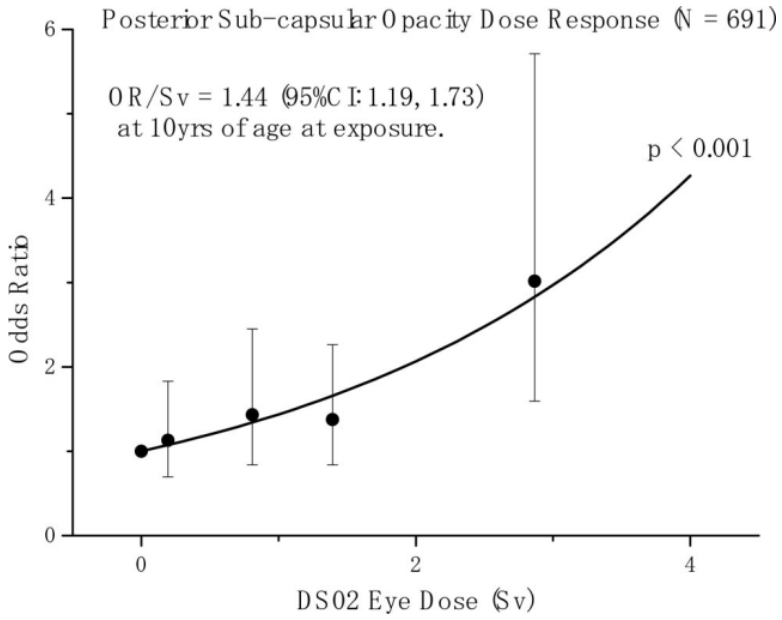
Lens opacities – some 50 yrs later in atomic-bomb survivors

Ophthalomologic examinations, Adult Health Study, 2000-02 (Nakashima, 2006)

	OR at 1 Gy	p	Threshold
Cortical cataract	1.30	0.002	0.6 Gy
PSC opacities	1.44	<0.001	0.7 Gy

Based on LOCS (Lens Opacity Classification System) III

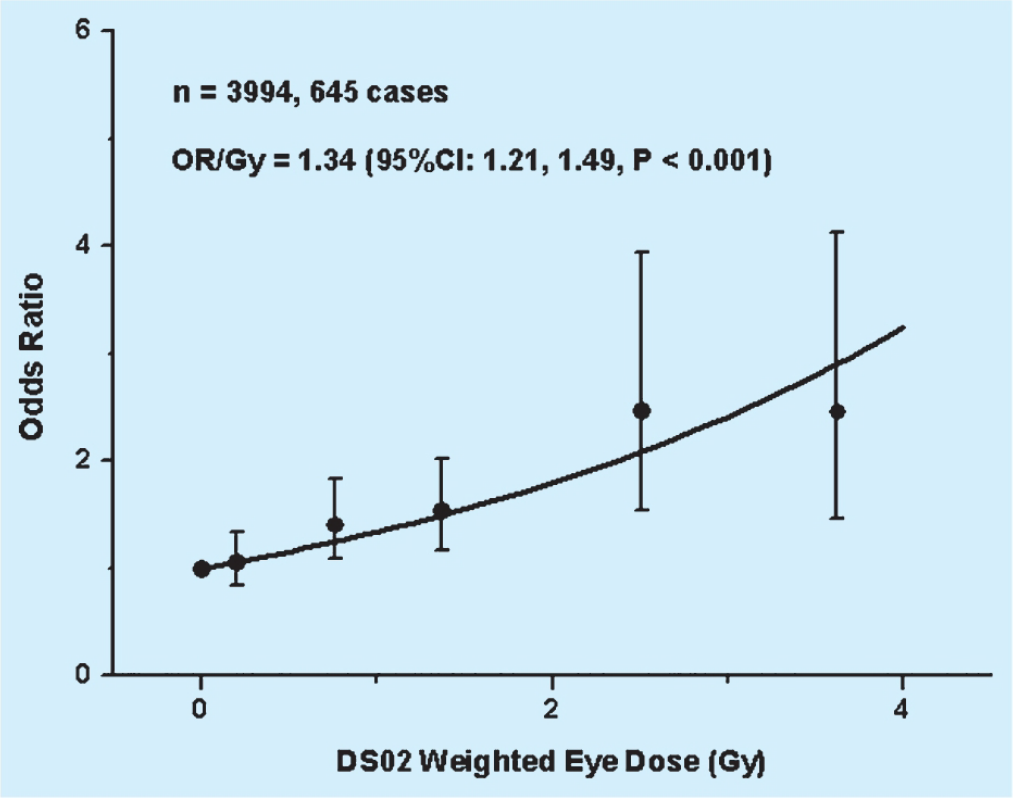
- Indication of a lower dose threshold level
- Emerging evidence of long-term effect on aging-related cataract (cortical cataract)



Postoperative Cataract, 2000-2002 (Nakashima, 2006)

OR at 1 Gy = 1.39

Best threshold estimate = 0.1 Gy



Chernobyl clean-up workers, Ukraine

8,600 clean-up workers examined for cataract 12-14 years after the accident (Worgul, 2007)

		m Gy					
Cataract	OR at 1 Gy	0-99	100-	250-	400-	600-	800+
Early PSC (Stage 1)	**1.42**	1.0	0.90	0.93	**1.20**	1.24	**1.72**
Adv opacities (Stages 2-5)	1.82	1.0	1.23	1.80	**2.56**	1.76	1.65
Cortical opacities (Stage 1)	1.51	1.0	0.89	1.00	1.07	**1.42**	**1.59**

Cataract – other studies

Exposure type	Supporting a lower or zero threshold	Questioning a lower or zero threshold
Diagnostic procedures	1	1
Radiotherapy	3	1
Residents of contaminated buildings	1	
Nuclear plan workers	3	4

Statement on Tissue Reactions
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(2) The Commission has now reviewed recent epidemiological evidence suggesting that there are some tissue reaction effects, particularly those with very late manifestation, where threshold doses are or might be lower than previously considered. For the lens of the eye, the threshold in absorbed dose is now considered to be 0.5 Gy.

(3) For occupational exposure in planned exposure situations the Commission now recommends an equivalent dose limit for the lens of the eye of 20 mSv in a year, averaged over defined periods of 5 years, with no single year exceeding 50 mSv.

LSS non-cancer mortality data (Shimizu, 1992)